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▲ 1.16 Radiotracer Imaging: Basic Principles and Exemplary Findings in Neuropsychiatric Disorders

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Radiotracer imaging can be understood from the two components of its name. *Radio* refers to the use of unstable atoms that decay and release radiation, which is detected after it leaves the body. *Tracer* refers to the fact that the radioactive compound is almost always administered in *trace* amounts that are too low to cause any pharmacological effects. Many of the principles of radiotracer methods derive from George de Hevesy, who received the Nobel Prize in chemistry in 1943 for the use of radioactive compounds to mirror the disposition of naturally occurring cognate nonradioactive compounds. For example, tritium-labeled glucose given in trace amounts can be used to monitor the disposition and metabolism of nonradioactive glucose present in much higher concentrations. The radioactive compound is typically administered in tracer doses, so that it does not significantly increase the total amount or concentration of the cognate compound. That is, the radiotracer accurately reflects the disposition of the cognate compound without significantly altering the endogenous situation. Because the radiotracer is merely a proxy for the cognate nonradioactive compound, why not directly measure the nonradioactive compound itself? There are two major reasons: (1) the feasibility of external measurements and (2) the high sensitivity of radiotracer methods. The direct measurement of nonradioactive glucose, for example, would presumably entail a sampling of the tissue and the use of an in vitro analytical method. Although blood can easily be used to obtain these measures, sampling directly in the brain would be problematic, because it is safely ensconced in the skull, and because such sampling might cause damage to brain tissues. In comparison, the γ-rays emitted by radiotracers travel through the skull, and nuclear medicine cameras are used to obtain external γ-ray measures. Second, radioactivity can be measured in low concentrations compared to many other analytical chemistry techniques. That is, radiotracer methods have high sensitivity. For example, the sensitivity of in vivo radiotracer imaging with positron emission tomography (PET) is approximately 10^{-12} to 10^{-14} mol. In comparison, the in vivo nuclear magnetic resonance (NMR) techniques described in the previous chapter have a sensitivity of approximately 10^{-4} mol. For example, in vivo NMR can measure brain levels of γ-aminobutyric acid (GABA) (present in mmol concentration) but lacks the sensitivity to measure most proteins in the brain that are often present at concentrations of less than 10^{-9} mol.

The two typical radiotracer methods used for neuroimaging are PET and single photon emission computed tomography (SPECT). Both are *tomographic* techniques, meaning that they can be used to reconstruct multiple image *slices* from successive depths in the brain. These tomographic methods differ from *planar* methods, such as X-ray imaging, in which, for example, the chest X-ray melds visual images of anterior bones into the same plane as images of posterior bones, resulting in a single, flat image. This chapter reviews the different types of radioactivity used in PET versus SPECT. PET uses a positron (i.e., nuclear particle) emitter, and, when positrons collide with electrons, two photons (i.e., two γ-rays) are released. In contrast, SPECT uses a nuclide that decays with the release of a single high-energy photon.

ADVANTAGES AND DISADVANTAGES

PET and SPECT have advantages and disadvantages relative to other neuroimaging modalities. Because both are radiotracer techniques, they have high sensitivity, with PET being approximately 100 times more sensitive than SPECT. Another advantage is pharmacological specificity. For example, a radioactive PET tracer can be made that binds to a small percentage of dopamine type 2 (D_2) receptors. Such a tracer, when used in conjunction with proper tracer methodology, can measure the total population or density of such receptors in a target region. PET probes can be made with such great specificity that they only bind to D_2 receptors and not to other subtypes of dopamine receptors, but, certainly, they also do not bind to other unrelated receptors, such as those for serotonin (5-HT). However, despite the positive aspects of sensitivity and pharmacological specificity of PET and

SPECT imaging, their two major disadvantages are limited resolution and radiation exposure. In the 1980s, early PET and SPECT cameras provided spatial resolutions in the range of 1 to 2 cm. Improvement has been made, as current commercial cameras now provide a resolution of approximately 3 to 5 mm for PET and 7 to 10 mm for SPECT. Nevertheless, these resolutions are still inferior in contrast to magnetic resonance imaging (MRI) (<1 mm). Another disadvantage of radiotracer techniques is that subjects are exposed to radioactivity. Exposures to radioactivity for clinical nuclear medicine procedures are not specifically regulated. In contrast, the vast majority of PET and SPECT imaging of psychiatric patients is for research purposes. Agencies of the federal government, such as the U.S. Food and Drug Administration (FDA) and Nuclear Regulatory Commission (NRC), as well as international agencies, have established guidelines (although not consistent) on the levels of radioactivity that provide a small, yet acceptable, risk of exposure for research subjects. However, this topic remains controversial among scientists and is also inflammatory among the lay public. Although all aspects of this dispute cannot be adequately reviewed here, certain generalizations can be made. First, most people in the general population do not understand that radiation exposure occurs to all of us—at the rate of approximately 1 mrem (millirem, a measure of radiation dose) per day from cosmic sources. Furthermore, the risk of radiation exposure during PET and SPECT scans can only be estimated, not immediately assessed. The levels of exposure during these procedures are far too low to cause immediate effects, such as radiation burn or radiation sickness. Instead, the most serious biological side effect is a potential increase in the likelihood of cancer (especially leukemia and lymphoma) that may develop as much as 10 to 30 years later because of radiation-induced mutations in deoxyribonucleic acid (DNA). There is a great deal of debate among scientists as to whether typical exposures of PET or SPECT actually increase the rate of developing cancer. However, there is consensus that, if the rate of cancer is increased, it is quite small and could only be measured in prospective studies by using extraordinarily large sample populations. For example, current statistics indicate that approximately one in four Americans dies of cancer. If radiotracer imaging increases this death risk, it is probably on the order of approximately 0.1 percent. This suggests an increase from 25 to 25.1 percent. Statistically significant measurement of such a small increase would require a study with a large sample size, and the existing prospective studies have been too small to detect any effect. Thus, current risk estimates have largely relied on follow-up studies of World War II survivors of Hiroshima and Nagasaki and have been calculated by using a linear back-extrapolation of data from persons with much higher levels of exposure with significantly increased rates of cancer. However, this back-extrapolation has been the crux of much controversy, and some scientists feel that a linear extrapolation is not appropriate. In contrast to estimates yielded by back-extrapolation, one school of thought (called *hormesis*) cites a substantial body of data from plants and animals that indicate low-level radiation exposure actually decreases genetic malformations by inducing the synthesis of DNA repair enzymes. In the end, psychiatrists must understand and then appropriately communicate to their research subjects that the increased risk of developing cancer, if it exists, is quite small and has not yet been adequately measured in prospective studies.

PSYCHIATRY FOLLOWS NEUROLOGY AND RADIOTRACER IMAGING FOLLOWS MRI

As a broad generalization, psychiatry's use of neuroimaging has largely followed and mirrored that in neurology. In a similar manner, PET and SPECT imaging modalities have followed and mirrored MRI applications. The first generalization can be seen in the clinical use of MRI in neurology. MRI has well-established usefulness for the diagnosis of disorders, such as stroke and multiple sclerosis (MS). The clinical usefulness of MRI for psychological disorders is still quite limited but is, nonetheless, following the example set by neurology. As described in the previous chapter, structural MRI research has demonstrated that many psychiatric illnesses, including schizophrenia, depression, and posttraumatic stress disorder (PTSD), are associated with structural abnormalities of the brain. Such findings have been shown to be statistically significant when comparing groups of subjects (e.g., patients vs. controls) but have not yet achieved usefulness for individual patients. In a similar manner, radiotracer imaging was initially applied largely to neurological patients (such as central nervous system [CNS] tumors, stroke, Alzheimer's disease, and Parkinson's disease), and psychiatry has followed suit with comparable studies in their patient population. Thus, psychiatry's use of MRI and radiotracer imaging has followed models initially applied in neurology.

Similarly, radiotracer imaging appears to follow the path of MRI. Structural MRI was initially used only for research purposes but then demonstrated clear superiority to computed tomography (CT) imaging of the brain. FDA approval of clinical use of MRI markedly stimulated technological advancement in the 1980s. The resolution and speed of image acquisition was improved, and, today, at least one MRI scanner can be found in almost every medium-sized to large hospital in America. The prevalence of these devices in university hospital centers allowed faculty to quickly implement functional MRI (fMRI) research studies when that technique was developed in the 1990s. Insurance reimbursement of the structural MRI scans served to inspire commercial interest and brought further improvements in the technology, which ultimately spurred the widespread acquisition of these devices worldwide. Comparatively, PET imaging has undergone a slower, more localized evolution of acceptance into clinical and commercial realms, and, until recently, it served only as a research tool. However, in the late 1990s, the FDA approved PET imaging of increased glucose metabolism for the localization of several primary tumors and their metastases. Subsequently, approval of reimbursement by insurance companies and the federal government's Center for Medicare and Medicaid Services (CMS), formerly the Health Care Financing Administration, led to improvements in PET technology, and it is now widespread in the United States. If a medium-sized hospital does not currently have a PET camera, it is likely considering its acquisition or has made plans for routine visits by a mobile PET device in a large truck. This recent expansion in PET technology was driven by clinical usefulness for oncology and has made this modality widely available for research. Analogous to fMRI development in existing MRI centers, one can now expect a marked expansion of research neuroimaging with PET.

CHALLENGES

A recent wave of medical specialties and general research fields have glibly, and even sometimes paradoxically, attached the word *molecular* to their professional designation to enhance prestige. It seems that *molecular neurobiology* is more fashionable, and perhaps more futuristic, than mere *neurobiology*. Some in psychiatry have even adopted the oxymoron *molecular psychiatrist* as their preferred title. With due acknowledgment of its fashionably excessive usage, the authors believe that radiotracer imaging could be legitimately characterized as *molecular imaging*. Despite the fact that there is no universally accepted definition of the phrase, this two-word title has recently been adopted by at least two new scientific societies, a few new journals, and many university departments. A reasonable stab at

the definition would posit that the targets to be imaged are specific molecules—for example, specific proteins, fatty acids, carbohydrates, or nucleic acids. In the case of neuroimaging, the targets have been almost exclusively protein molecules (such as a specific enzyme, receptor, or transporter). Conversely, relatively little work has been done to measure fatty acids and carbohydrates in the brain, and radiolabeled probes for nucleic acids are not currently useful for brain imaging, because the probes themselves are charged and cannot cross the blood–brain barrier or cell membranes. Thus, radiotracer imaging in the brain could be defined as a subset of molecular imaging that focuses on specific proteinaceous molecular targets. Despite the lack of consensus on the definition of *molecular imaging*, it should surely be contrasted with *functional imaging*, which is commonly understood to measure localized neuronal brain activity. Because of the collinear relationship between neuronal activity and localized blood flow, oxygen extraction, and glucose use, increased neuronal activity can be implied using PET and fMRI. Because blood and glucose are present in high concentrations in brain, high sensitivity is not required for such measurements. Thus, most functional neuroimaging studies have switched from PET to fMRI, which has no radiation exposure and much better spatial and temporal sampling resolution. In summary, *molecular imaging* is used to reflect specific molecular targets and is contrasted with *functional imaging* of local neuronal activity.

With this definition of radiotracer imaging as *molecular imaging*, the major challenges to the field become more obvious. Which specific protein targets in brain should be measured and can this be done? PET imaging in schizophrenia exemplifies these dilemmas. Many initial PET studies in schizophrenia in the 1980s and 1990s focused on the dopamine D_2 receptor, because clinically useful antipsychotic agents act as antagonists at this site, and because PET tracers could be relatively easily developed as radiolabeled analogs of neuroleptic medications. Numerous controversial studies were performed, but the current consensus is that patients with schizophrenia have minimal, if any, increase in dopamine D_2 receptors and that such alterations are certainly not required to develop the disorder. So, which proteins should now be measured in schizophrenia? In addition, the development for PET probes for these new protein targets is expensive and time consuming.

The usefulness of radiotracer imaging in psychiatry is based on the assumptions that protein abnormalities are associated with psychiatric illnesses and that medications need to be developed for these protein targets. Both of these assumptions are adequately justified to devote personal careers and major resources to this area. The challenges that are now faced are numerous. Broadly trained and clever scientists are needed to determine relevant research findings from basic neurobiology that justify the effort to translate such measurements to living subjects with PET. Substantial medicinal chemistry and radiochemistry efforts are needed to develop new PET probes for selected protein targets. Clinical nuclear medicine expertise and sophisticated methods of digital image quantitation are required to evaluate the safety and efficacy of new PET probes. Finally, almost a new breed of psychiatrists must be trained in neuroimaging techniques to be able to design and to apply radiotracer imaging methods. In fact, if clinical usefulness is demonstrated for radiotracer imaging in psychiatry, subspecialty training in neuroimaging may be required for some psychiatrists, just as neuroradiology is a subspecialty in that field of medicine.

This overview has now come almost full circle, and the purpose of the chapter has become clear. That is, this text is designed as an introduction to the field of molecular neuroimaging, which offers great promise to understand the protein abnormalities that underlie psychiatric illness, in the hope that this knowledge will enhance diagnosis, guide treatment, and assist in the development of improved treatments.

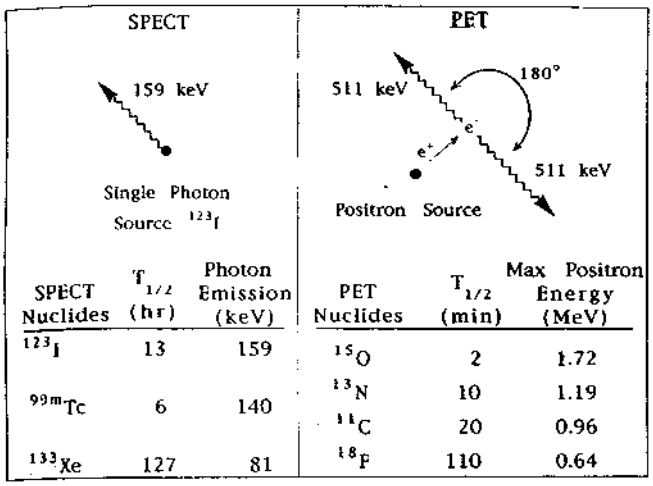
BASIC PRINCIPLES

In PET and SPECT, a biological process of interest is studied by synthetically incorporating a radionuclide into a molecule of known physiological relevance. The so-called radiopharmaceutical is then administered to a patient by inhalation, ingestion, or, most commonly, intravenous (IV) injection. As radioactivity distributes within the subject, the radiotracer's uptake into the brain is measured over time and is used to obtain information about the physiological process of interest. Because of the high-energy γ-ray emissions of the specific isotopes used and the sensitivity and sophistication of the instruments used to detect them, the two-dimensional distribution of radioactivity within a brain slice may be inferred from information obtained outside the head. For this reason, PET and SPECT are referred to as *emission tomographic* (from the Greek *tomos* for cut) techniques. (The data of PET and SPECT are actually collected as three-dimensional volumes, and two-dimensional images can be created on any plane.) In contrast to more conventional radiographic methods, such as a chest X-ray, in which an external source of radiation merely casts a shadow of the body's organs and cavities onto a planar film, PET and SPECT rely on more sophisticated principles to produce three-dimensional information. To understand this process, a basic understanding of the physics of photon emission is required.

Physics of Photon Emission

Radioactive decay is a process in which an unstable nucleus transforms into a more stable one by emitting particles or photons, or both, and releasing nuclear energy. For the radionuclides used in PET, a proton is converted to a neutron, and a particle called a positron (denoted e^+ or β^+) is emitted. A positron may be thought of as the antimatter equivalent of an electron, possessing identical mass but opposite charge. When ejected from the nucleus, a positron travels until it collides with an electron. This collision results in the annihilation of both particles and the conversion of mass into energy (Fig. 1.16–1). The energy produced has a characteristic profile consisting of two γ-photons (rays) of equivalent energy (511 keV) and opposite trajectory (180 degrees apart, although this is actually not exactly 180 degrees; see the following discussion). These dual photons distinguish PET from SPECT and have implications for camera design. The most commonly used positron-emitting nuclides in PET include carbon-11 (^{11}C), nitrogen-13 (^{13}N), oxygen-15 (^{15}O), and fluorine-18 (^{18}F).

PET scanners take advantage of the unique spatial signature of "back-to-back" photons by using a method known as *coincidence detection* to locate the source of an annihilation event, (Fig. 1.16–2). Coincidence detection is an efficient technique and contributes to PET's superior sampling rates, sensitivity, and spatial resolution compared to those of SPECT. In a typical configuration, a PET scanner consists of a circular array of highly sensitive scintillation detectors that surround the head. These detectors are made of dense crystalline materials (e.g., bismuth germanium oxide [BGO], sodium iodide, or cesium fluoride) that trap the invisible, high-energy γ-rays and convert them to visible light. This brief flash of light is then converted into an electrical pulse by an immediately adjacent photomultiplier tube (PMT), and the electrical pulse is then registered by the scanner's computer. When the scanner detects two electronic signals from two radiation detectors that coincide (to within 3 to 10 nanoseconds, for practical purposes), an



SPECT Nuclides	$T_{1/2}$ (hr)	Photon Emission (keV)
^{123}I	13	159
^{99m}Tc	6	140
^{133}Xe	127	81

PET Nuclides	$T_{1/2}$ (min)	Max Positron Energy (MeV)
^{15}O	2	1.72
^{13}N	10	1.19
^{11}C	20	0.96
^{18}F	110	0.64

FIGURE 1.16–1 The decay of a single photon emission computed tomography (SPECT) radiopharmaceutical results in the emission of a high-energy photon directly from the radionuclide. In contrast, the decay of a positron emission tomography (PET) radiopharmaceutical results in the emission of a positron (e^+), which travels a variable distance before annihilating with an electron (e^-), which then yields two 511-keV photons at 180-degree angles to each other. The distance traveled by the positron decreases the resolution of PET images, when using the typical nuclides listed, by 0.2 to 1.3 mm, with resolution measured as full width at half maximum. The longer-lived SPECT radionuclides emit single photons of different energies, whereas the PET radionuclides consistently yield two photons of 511 keV. ^{11}C, carbon-11; ^{18}F, fluorine-18; ^{123}I, iodine-123; ^{13}N, nitrogen-13; ^{15}O, oxygen-15; $T_{1/2}$, terminal half-life; ^{99m}Tc, technetium-99m; ^{133}Xe, xenon-133.

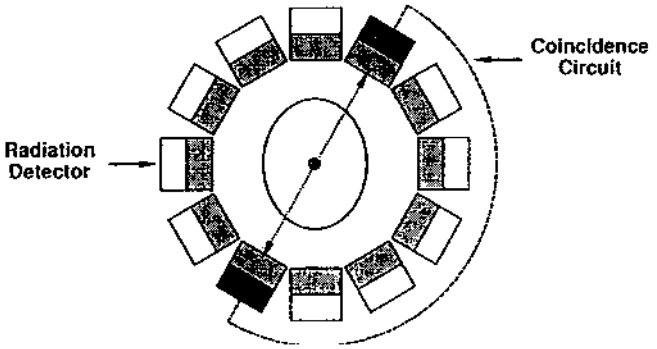


FIGURE 1.16–2 A positron emission tomography scanner consists of a ring of radiation sensors that are designed to detect the simultaneously emitted, characteristically "back-to-back" (180 degrees apart) dual photons that are created by the annihilation of a positron and an electron. Opposing detectors are electronically coupled to form a coincidence circuit. Thus, when separate scintillation events in paired detectors coincide, an annihilation event is presumed to have occurred at some point along a line connecting the two. This information is registered by a computer and later is used to reconstruct images using the principles of computed tomography. (From Malison RT, Laruelle M, Innis RB. Positron and single photon emission tomography: Principles and applications in psychopharmacology. In: Bloom F, Kupfer D, eds. *Psychopharmacology: The Fourth Generation of Progress*. New York: Raven Press; 1995, with permission.)

annihilation event is presumed to have occurred at some point along an imaginary line connecting the detectors. In contrast, single events are ignored. Although any two crystal detectors may be activated by coincident photons, the most straightforward conceptual configuration for a PET camera is one in which only opposing detectors are electronically connected. Although it is the case that two unrelated photons from spatially separate annihilation events can reach opposing detectors concurrently, such accidental coincidences are much less frequent than true ones. Nevertheless, random coincidences constitute one source of the background noise in PET images.

Because PET detects the site at which a positron annihilates and not the site of its emission, there exists an intrinsic theoretical limit on the spatial resolution of PET. Specifically, a positron generally travels a finite distance before coming to rest in a tissue and colliding with an electron (positron range). Thus, an annihilation typically occurs some distance away from the site of radioactive decay. This distance is proportional to the positron's average kinetic energy as it is emitted from the nucleus and is characteristic of the specific isotope used (Fig. 1.16–1). For example, the average range for ^{11}C decay is 1.1 mm. An additional limitation placed on PET is that photons are emitted at an angle slightly different than 180 degrees (noncollinear annihilation). The residual momentum of the electron pair at annihilation results in γ-rays being emitted with a small deviation from the assumed 180 degrees. Thus, positron range and noncollinear annihilation are factors that theoretically limit PET's achievable spatial resolution.

For the radionuclides used in SPECT, a somewhat opposite type of radioactive decay occurs. Instead of a proton-rich radionuclide ejecting a positron (i.e., e^+), it "captures" an orbiting electron (denoted e^-). Once again, the net result is transformation of a proton into a neutron. For some radionuclides, the radioactive progeny of this process remains in a residually excited, so-called metastable state. With the dissipation of this metastable arrangement, the daughter nucleus achieves a ground state, and a single γ-photon is produced. Thus, SPECT uses isotopes that decay by electron capture or γ-photon emission, or both, including iodine-123 (^{123}I) and the long-lived metastable nuclide technetium-99m (^{99m}Tc). A theoretical limit on spatial resolution, which is comparable to the positron range, exists for SPECT, because the site of γ-photon emission and the site of radioactive decay are synonymous.

The emission of only a single photon fundamentally distinguishes SPECT from PET and necessitates an intrinsically different approach to ascertaining the origin of a decay event and, therefore, camera design. Specifically, SPECT uses a method know as *collimation* (Fig. 1.16–3). In a manner analogous to the effects of a polarizing filter for visible light, a collimator is a physical filter that permits only γ-rays of a specific spatial trajectory to reach the SPECT scanner's detector. Most commonly, a collimator is a lead structure that is interposed between the subject and the radiation detector. The collimator contains many holes of sufficiently long and narrow dimension, so that only photons of a parallel trajectory are allowed through. In contrast to parallel photons, γ-rays that deviate slightly are absorbed by the lead and go undetected (Fig. 1.16–3). Different collimators (e.g., parallel, fan-beam, and cone-beam) have holes of differing orientations (e.g., perpendicular to the detector, focused in two dimensions, and focused in three dimensions, respectively). Given a known geometric configuration for the specific collimator's holes, the original path of a detected photon is linearly extrapolated. As might be imagined, collimation is much less efficient than coincidence detection, because many potentially informative photons are lost. Although the sensitivity of SPECT has been largely overcome by advances in collimator design and increases in the number of detectors surrounding the body, the sensitivity is still much lower than that of PET, as described in the introduction. As one can imagine from the difference between coincidence detection (PET) and collimation (SPECT), PET has higher spatial resolution.

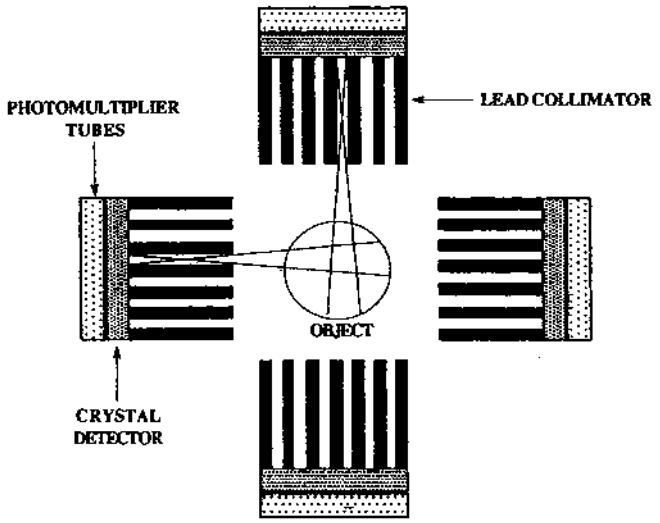


FIGURE 1.16–3 The method of image reconstruction from back projection in single photon emission computed tomography uses a collimator placed between the object and the crystal detector. The area of the object that is viewed by the underlying detector is decreased by having longer and narrower holes in the collimator. By moving the detector-collimator complex around the object, multiple views are obtained and provide the primary data for image reconstruction.

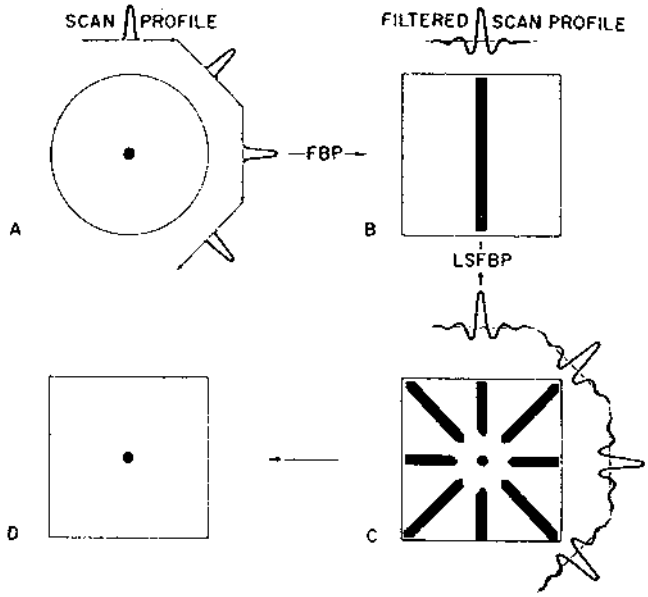


FIGURE 1.16–4 Example of Fourier-based reconstruction technique, linear superposition of filtered back-projection (LSFBP). Detector readings are zero, except when a small object at center is encountered. **A:** Object and scan profiles. **B:** Single filtered scan profile projected back across the cross-sectional plane. **C:** Four filtered scan profiles projected back across the plane and added together (superposition). **D:** Image produced when sufficient angles are used to remove defocusing. (From Phelps ME, Hoffman EJ, Gado M, Ter-Pogossian MM. Computerized transaxial transmission reconstruction tomography. In: DeBlanc HJ Jr, Sorenson JA, eds. *Noninvasive Brain Imaging, Computed Tomography and Radionuclides*. Reston, VA: Society of Nuclear Medicine; 1975, with permission.)

Image Reconstruction Although the nature of photon emission and detection are different in PET and SPECT, both techniques rely on the same principles of CT when translating information about photon paths into brain images (Fig. 1.16–4). Briefly, CT is based on the premise that an appreciation of an object's two- or three-dimensional distribution in space may only be inferred by viewing it from multiple vantage points (Fig. 1.16–4A). More specifically, because information about a photon's direction, not depth, is known, views of photon trajectories from multiple angles around the entire head are required. In PET and SPECT, such a set of measurements from a given angle or viewpoint is referred to as a *projection* or *scan profile* (Fig. 1.16–4B). A ring of essentially contiguous radiation detectors in a PET scanner provides multiple scan profiles in this modality. In contrast, SPECT cameras usually rely on several (typically two to four) detector "heads" that rotate around the subject in synchrony, collecting data over an entire 360 degrees. A picture of the distribution of radioactivity within a given brain slice is then inferred by retracing or *back-projecting* the trajectories (typically thousands) of γ-rays across the field of view for every imaging angle (Fig. 1.16–4C). Conceptually analogous to the simple childhood puzzle in which numbers in a square grid (e.g., 3 × 3) are inferred from their sums along each row, PET and SPECT images require fast computer coprocessors and efficient mathematical algorithms (fast Fourier transformations) to handle the considerably larger matrices (e.g., 128 × 128 or 256 × 256 elements) of radiation density values and the correspondingly more intensive calculations. In this manner, individual radiation values (i.e., counts of detected events) are determined for each cell of the matrix (also known as a picture element or *pixel*), corresponding shades of color are assigned, and an image of the distribution of radioactivity within the brain is produced.

Despite its complexity and computational intensity, back-projection is an imperfect process and, in fact, introduces known artifacts into the images themselves. As the back-projection algorithm retraces a photon's path, it cannot be sure of the actual point of decay. Therefore, the algorithm is forced to assume an equal probability of radioactive decay and, hence, radiation value for every point along the line of trajectory. Areas of the brain in which radioactivity is highly concentrated stand out as many trajectories from multiple projections are superimposed and their probability values are summed (Fig. 1.16–4C,D). In the process, however, those areas containing no radioactivity now bear the statistical imprint of the algorithm's guess. Thus, small, but finite, values are ascribed to areas at which none should exist. By increasing the density of spatial sampling through greater numbers of projections, the impact of these spurious values on image quantitation can be minimized but not eliminated. Therefore, a filter is still required to restore quantitative accuracy to images by erasing counts in those areas that should have none. Several filters have been developed (e.g., Ramp, Butterworth, and Hanning) in an effort to overcome these limitations, and these techniques remain the mainstay of the field of image reconstruction. Although the considerations involved in the choice of a filter are beyond the scope of this chapter, suffice it to say that trade-offs exist with respect to their relative impact on spatial resolution and noise amplification, and filter selection depends on the imaging context. Alternative reconstruction methods (e.g., restorative and iterative techniques) are the current focus of much research, and simple filtered back-projection is likely to be superseded by more quantitatively accurate methods in the near future.

Factors Affecting Image Quantitation Several physical factors affect the quantitative accuracy of PET and SPECT images. Among these are the statistics of radioactive decay, attenuation, scatter, limited spatial resolution, and partial volume effects.

Statistics of Radioactive Decay Mathematically, radioactive decay is described by an exponential curve. The rate at which a specific radionuclide decays is expressed in terms of its radioactive half-life ($T_{1/2}$) value, a parameter defined as the time required for one-half of the radioactive atoms to decay. Values of $T_{1/2}$ vary between species and are characteristic of a given nuclide. The characteristic $T_{1/2}$ values of several commonly used PET and SPECT isotopes are listed in Figure 1.16–1. Although a given isotope's $T_{1/2}$ is constant, the nature of radioactive decay is intrinsically statistical. This phenomenon is most readily conceptualized by imagining an isotope of infinite $T_{1/2}$ (i.e., unchanging levels of radioactivity). In struggling to measure the precise amount of radioactivity during a fixed period of time, one's efforts invariably lead to variations in the individually recorded values. Only by taking the statistical average of multiple measurements is the true amount of radioactivity (and $T_{1/2}$ value) inferred. The variation in sampling derives from the intrinsic probabilistic nature (mathematically described by a Poisson distribution) of radioactive decay and the random fluctuation in individual decay events from moment to moment, and it occurs irrespective of detection method.

The manifestations of this effect are most readily appreciated by imaging an object that contains a uniform concentration of radioactivity. The Swiss cheese appearance of the resulting images is the spatial equivalent of this temporal variation in PET and SPECT images. The probabilistic inaccuracies or *statistical noise* introduced is, by virtue of its random nature, easily surmountable through the collection of more counts. Longer sampling times and greater instrument sensitivity are the principal ways in which counting statistics are improved. In the former, longer acquisition times improve statistical noise at the expense of temporal resolution. Conversely, increased sensitivity (e.g., larger collimator holes in SPECT) is traded for poorer spatial resolution (i.e., because slightly-less-than-parallel photons are detected).

Photon Attenuation Although the high energies of photons emitted by PET and SPECT nuclides enable their penetration of brain structures, a significant number of γ-rays escape detection by both types of scanners based on their interactions with surrounding tissues. These interactions fall into one of two general categories—Compton scattering and photoelectric absorption. In Compton scattering, a collision occurs between the photon and an atomic electron. The photon is deflected from its original trajectory and, in the process, loses a fraction of its original energy. Alternatively, in photoelectron absorption, the photon's energy is completely absorbed by the atom, and an electron may be ejected from its orbit. For the latter reason, γ-radiation is said to be *ionizing*.

Because the chances of scatter or absorption decrease with increasing photon energy and increase with distance, photon attenuation is energy and depth dependent. On both counts, PET has distinct advantages. Because photons in PET have higher energies (i.e., 511 keV) than those in SPECT (typically 80 to 160 keV), they are less prone to attenuation (Fig. 1.16–1). Nevertheless, activity at the brain's center is disproportionately underestimated (by roughly four to five times) in comparison to its surface for PET and SPECT. Compensating for undetected photons is therefore crucial for comparing radioactive densities in different brain regions. The most commonly used method with SPECT is *uniform* attenuation correction. In uniform attenuation correction, an ellipse is fitted to the brain's contour, and the same attenuation value (typically equal to that of water) is assigned to all points within the ellipse. A commonly used method for attenuation correction in PET (and with some recent SPECT devices) is *nonuniform (measured)* attenuation correction, which relies on a preceding transmission study similar to a CT scan. An external source of radiation is transmitted through the subject's head, creating a precise attenuation map for that individual. Because the sizes and shapes of patients' heads vary, and because the attenuation properties of bone, tissue, fluid, and air differ, such an approach has clear theoretical advantages.

Photon Scatter In PET and SPECT, instrumentation and image reconstruction are based on the underlying assumptions that detected photons retain their linear paths. As noted previously, however, Compton effects cause photons to deviate from their original trajectories. Although these photons lose energy to atoms in the tissue, many scattered photons retain sufficient energy to enable their escape from the brain. The detection of scattered events therefore leads to errors in image reconstruction as a result of false assumptions about the photon's original path. Much like accidental coincidences, scattered photons increase the background noise and compromise image contrast.

Because radionuclides emit photons of a known energy, scattered photons may be distinguished from true ones by the loss of energy they sustained from collisions with electrons. In an attempt to exploit this principle, PET and SPECT cameras measure the energy spectrum of their detected photons. In practice, however, accurately discriminating between true and scattered photons is often difficult. First, the energy resolution of current PET and SPECT scanners is limited. Second, the photopeak energies of true photons are not identical but rather normally distributed around a mean value. Thus, scattered and photopeak photons inevitably overlap in their energy distributions. Current algorithms subtract a *scatter fraction* from the photopeak counts in an attempt to compensate for this problem. However, these methods have obvious limitations. As for attenuation correction, advances in scatter correction offer the promise of incorporating a priori information about the head's structure and density in achieving more faithful image reconstruction.

Spatial Resolution In contrast to the fine visual detail seen in MRI, pictures created using SPECT and PET appear blurred. The visual sense of imprecision is the qualitative consequence of limited spatial resolution. Equally important, however, is the quantitative impact of finite resolution on the measured radioactivity in individual brain regions. The latter, so-called *partial volume effects* have important consequences for image quantitation and require a clearer understanding of spatial resolution and its definition.

In PET and SPECT, *spatial definition* is defined in practical terms—the distance by which two objects must be separated to perceive them as discrete (Fig. 1.16–5). In a SPECT or PET camera with perfect resolution, a point source of radioactivity would be depicted as a vertical line of infinitely narrow width. In such an ideal device, two point sources could be distinguished from each other as long as they were not superimposed. In the real world, however, PET and SPECT scanners perceive the radioactivity from such a point source as a gaussian curve. The radioactivity from the point is spread out. This so-called point spread function characterizes a camera's resolving capacity. This spatial diffusion of imaged radioactivity is expressed in terms of the *full width at half maximum* (FWHM), or the width of the gaussian curve at one-half of the curve's peak activity. The FWHM is the parameter most commonly used to define resolution in emission tomography, because this is the distance at which the peaks of both sources become distinguishable from one another (Fig. 1.16–5).

Excluding issues of positron range, image resolution is primarily influenced by issues of instrumentation. For example, the precision of collimation, the number and size of detectors, and the accuracy with which scintillation events are localized within the crystalline elements all contribute to limited spatial resolution. In the case of

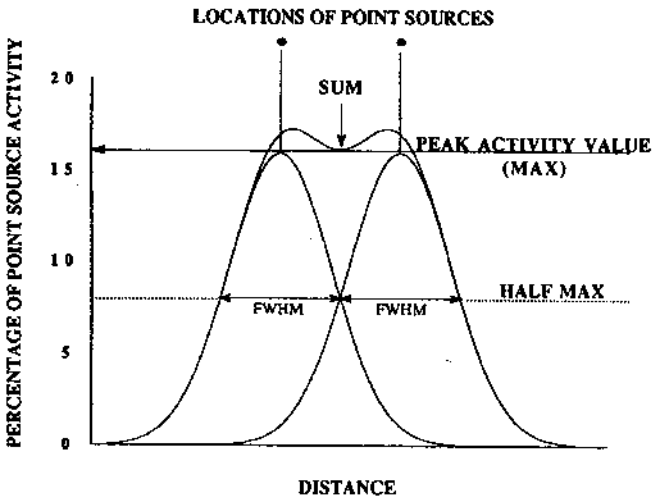


FIGURE 1.16–5 The limited resolution of positron emission tomography and single photon emission computed tomography cameras blurs the activity of single point sources into adjacent regions with no activity. Viewed in just one dimension, a point source is visualized by the camera as a gaussian curve. Resolution is defined as the width of the curve at half maximum measured peak levels (full width at half maximum [FWHM]). For two point sources of equal intensity separated by a distance equal to the FWHM of the camera, the sum of the activities begins to show a modest decrease at the midpoint. Thus, two point sources separated by a minimum distance equal to the FWHM begin to appear as two separate points rather than just one.

PET, state-of-the-art devices have yielded resolutions close to the theoretical limits of accuracy (2 mm). However, the average PET and SPECT cameras are currently capable of 5 to 6 mm and 7 to 9 mm FWHM, respectively.

Partial Volume Effects In its simplest terms, partial volume effects create one of two problems for image quantitation: the appearance of radioactivity where there was none and the impression of less radioactivity than truly exists. For example, just as the brightness in a part of a room depends on the intensity and distance separating two lamps, so too does the measured radioactivity in a given brain region reflect the relative activity and proximity of nearby structures. Thus, brain regions having relatively lower concentrations of radioactivity appear "hotter" in PET and SPECT images as imaged activity "spills over" from adjacent (more active) areas. Conversely, as the size of a radioactive region becomes smaller than two to three times the FWHM, true activity is effectively diluted by nonradioactive areas within the field of resolution. In the latter case, regions containing equal concentration of radioactivity appear to have declining levels with decreasing size. Together, these two effects result in, by visual analogy, sharp peaks and steep canyons of brain activity being rendered as short hills and shallow valleys in PET and SPECT images.

Several approaches are currently taken to compensate for errors resulting from limited spatial resolution and partial volume effects. One method attempts to simulate errors created by partial voluming by creating a plastic model or phantom. Models can be designed to approximate the structures or activity distributions, or both, of interest in the brain. For example, finely machined, polycarbonate brain phantoms are commercially available that recreate the geometry of gray and white matter. Once imaged, regionally specific correction factors, or recovery coefficients, are derived that relate units of measured activity to known activity. Such methods, however, are unable to account for intersubject variations in brain anatomy, whether pathological or nonpathological. A more modern way to correct partial volume effect is to use structural information (e.g., CT or MRI scans) of individual subjects for quantifying functional information. More specifically, partial volume errors may be mathematically compensated for by registering a subject's MRI scan with his or her own PET or SPECT scan and incorporating a priori functional (e.g., relative blood flow ratios in gray and white matter) and physical information (e.g., a PET or SPECT camera's three-dimensional point spread function). Although more complicated than the former technique, the latter approach has obvious advantages for conditions, such as Alzheimer's disease, in which cortical atrophy is present.

Radiopharmaceuticals The versatility and sensitivity of PET and SPECT arise largely from the ability of talented radiochemists to synthesize a radiopharmaceutical of high chemical purity, high radioactive yield, and small mass dose. Expressed differently, to ensure that a specific biological system of interest is adequately measured, yet unperturbed, by the tracer, a high purity and high specific activity (expressed in units of radioactivity per chemical quantity; e.g., Ci/mmol) are paramount. However, the physical nature of radioactive decay and the short $T_{1/2}$ of most suitable radionuclidic species (Fig. 1.16–1) constantly challenge the radiochemist's efforts. Specifically, chemical yield generally improves with increasing reaction times; however, radioactivity (and specific activity) diminishes with increasing decay times. Thus, an optimal synthetic scheme is a balanced one in which chemical yield is maximized, radioactive byproducts are minimized, and the final product is capable of prompt purification. Given the high affinity of many radiopharmaceuticals (e.g., neurotransmitter receptor ligands) for their physiological targets, specific activities of greater than 1,000 to 2,000 Ci/mmol are generally required. Although most radiopharmaceuticals are still manually prepared by radiochemists racing against the clock of a nuclide's decay, a limited number of radiochemical syntheses are now automated and performed in robotically controlled hot cells (e.g., [^{18}F]-2-fluoro-2-deoxyglucose [(^{18}F)FDG]; [^{11}C]raclopride).

In the case of positron-emitting radionuclides (e.g., ^{15}O, ^{13}N, ^{11}C, and ^{18}F), the particularly short $T_{1/2}$ (2, 10, 20, and 109 minutes, respectively) has special implications for the design of PET imaging facilities. Most PET centers have an on-site cyclotron that generates radionuclides for real-time use. An exception to this is ^{18}F, whose nearly 2-hour $T_{1/2}$ permits a local regional facility to produce quantities for a large or nearby metropolitan center. The significant expense of a cyclotron (typically $1 million to $2.5 million) and its highly skilled support staff are relative disadvantages for PET. In contrast, SPECT isotopes, such as ^{99m}Tc ($T_{1/2}$, 6 hours), may be obtained from inexpensive molybdenum generators located in many hospital radiopharmacies. Alternatively, ^{123}I has a sufficiently long $T_{1/2}$ (13 hours) to permit centralized production at distant (>3,000 miles) commercial reactors. The radionuclide may then be delivered via overnight express mail and may still meet the radiochemical needs of high activity.

The choice of a candidate molecule for radiopharmaceutical development depends primarily on the physiological process that one is interested in studying. In the case of regional cerebral blood flow, relatively nonspecific, and often nonorganic, diffusible tracers may be used (e.g., the gaseous tracer xenon-133 [^{133}Xe]). In contrast, the measurement of aspects of brain neurochemistry requires much greater biochemical selectivity. Thus, PET and SPECT radiopharmaceuticals are most often naturally occurring substances, structural analogs, or ligands that selectively label a particular brain target. In this regard, PET has significant advantages over SPECT, because ^{11}C can be directly substituted for carbon-12 (^{12}C) in existing organic molecules

without altering their intrinsic biochemical properties. Alternatively, fluorine is frequently substituted for native hydrogen atoms without significant isotopic effects (e.g., [^{18}F]FDG). In contrast, SPECT nuclides (i.e., ^{123}I and ^{99m}Tc) are uncommon elements of organic substrates. The metallic nature and multiple valence states of ^{99m}Tc necessitate bulky complexing groups for its molecular stabilization. These barriers have largely limited the initial uses of ^{99m}Tc to nonselective processes (e.g., the blood flow agent [^{99m}Tc]-hexamethyl propyleneamine oxime [(^{99m}Tc)HMPAO]). However, ^{99m}Tc-labeled probes of the dopamine transporter (DAT) have recently been developed, and SPECT imaging has demonstrated appropriate labeling in human and monkey brains. Extension of these efforts is certain to result in the development of many other ^{99m}Tc-labeled probes in the future.

Many ^{123}I-containing radiopharmaceuticals have been developed as a result of rapid advances in iododemetallation procedures and increasing knowledge of the structure–activity relationships of pharmacologically active compounds. In fact, the lipophilic nature of ^{123}I may actually facilitate transfer across the blood–brain barrier and, in some instances, may improve affinity of the parent compound at its site of action. In particular, SPECT imaging of brain receptors and uptake sites with ^{123}I-containing radiopharmaceuticals is routine at many university medical centers.

Successful in vivo radiopharmaceuticals must fulfill several stringent pharmacokinetic criteria. Because a radiopharmaceutical must easily enter the brain, tracer binding to plasma proteins must be readily reversible, and its transport across the blood–brain barrier must be favorable. Although some tracers (e.g., [^{18}F]FDG) may have facilitated carriers, most ligands must be sufficiently lipid-soluble to permit passive diffusion across the blood–brain barrier. However, as tracer's lipophilicity increases, its *signal-to-noise* properties may be degraded as nonspecific binding increases. If lipophilicity is too high, passive diffusion across the blood–brain barrier is also impaired owing to increased binding to plasma proteins and blood cells. Therefore, a certain level of lipophilicity (typically a log D [log of ratio of radioligand in oil and water measured at pH 7.4] of 1 to 3 is required). Higher affinity is required to obtain higher levels of specific binding. Thus, lipophilicity (brain uptake and nonspecific binding) and affinity (specific binding) are important factors influencing an imaging agent's signal levels and signal to noise ratio. Lastly, tracer metabolism may also limit a ligand's in vivo usefulness. For example, rapid degradation, lipophilic radioactive metabolites, and pharmacologically active metabolites may all confound central measurements.

Small Animal PET and SPECT Imaging PET devices designed to image small animals, such as rodents, were brought into operation in the early 1990s. During the last few years, significant improvements in imaging devices and data processing algorithms, as well as the development of various strains of genetically modified mice, spurred a quickly growing interest in small animal imaging techniques in various fields besides nuclear medicine, including basic science, clinical medicine, and the pharmaceutical industry. These techniques provide valuable information from living animals that is hard to obtain using conventional in vitro procedures, such as homogenate receptor binding assay and autoradiography. However, one should be aware of current limitations of small animal imaging that are occasionally overlooked, such as high receptor occupancy by imaging ligands.

Although small animal imaging devices have reached a spatial resolution of FWHM 2 mm, autoradiography provides, and probably will continue to provide, information with greater spatial resolution. However, to perform autoradiography, animals must be sacrificed to prepare brain slices. Therefore, small animal imaging is particularly useful when performing repeated measurements within a single experiment or across multiple experiments on the same animals over time. Imaging studies are particularly valuable when availability of animals, such as genetically engineered mice, is limited.

In addition to repeated measurements, small animal imaging may also be useful to detect in vivo biochemical processes that are difficult to study using other techniques. For example, small animal imaging can be used to evaluate the usefulness of imaging agents that label amyloid plaques in mice that have been genetically engineered to overexpress amyloid plaques. Although radioligand binding to amyloid plaques can be confirmed by in vitro binding assay and autoradiography, it is difficult to study kinetic properties of the radioligand by sacrificing animals at multiple time points after radioligand injection. Desired properties of imaging agents are (1) rapid passage of blood–brain barrier, (2) quick washout of nonspecifically bound tracer, (3) low nonspecific uptake, and (4) dissociation of specifically bound tracer within the time frame for PET or SPECT scans. Fifty to 100 times more animals are required to obtain the desired information when sacrificing animals at multiple time points after tracer injection than with small animal imaging; thus, small animal imaging offers great advantage, as it is often difficult to obtain a large number of genetically engineered animals. However, it is important to note that small animal imaging does not completely replace the need for classic techniques. In the case of amyloid imaging, binding characteristics first need to be studied by in vitro binding assay and autoradiography. In vivo radioligand binding must be confirmed by sacrificing animals after ligand injection and examining the coincidence of radioactivity and amyloid plaque location on brain slices. Therefore, small animal imaging and classic procedures together provide the essential information. Another thing that should not be overlooked is that imaging data do not provide information on chemical properties of the radioactivity. For example, it is necessary to know if the radioligand produces labeled metabolites that enter the brain and increases nonspecific radioactive signals. To obtain such information, radioactive compounds in plasma and the brain must be analyzed with high-performance liquid chromatography.

Whole-body distribution studies are required to estimate radiation-absorbed doses. By imaging the whole body by using small animal imaging devices, such studies can be performed much quicker than the classic methods that entail dissecting individual animals. Additionally, use of high-resolution human imaging devices (e.g., CTI's HRRT) for small animal whole-body imaging is more efficient than using small animal PET devices, because several animals can be scanned at the same time.

Another use is the detection of in vivo biochemical processes. Reporter gene imaging is a common application for small animal imaging devices. The basic design of this technique is to deliver a fusion of a reporter and a therapeutic gene. Thus, one can indirectly monitor the transcription of the therapeutic gene by using a radiolabeled tracer that is specifically metabolized by or that specifically binds to the product of the reporter gene. The final goal of these techniques is to monitor gene therapy in humans. These techniques were recently modified to noninvasively detect endogenous biological processes. Endogenous gene expression is monitored by administering transgenes containing endogenous promoters fused to a reporter gene. The transcription of the fused gene is then expected to mimic that of endogenous genes connected to the same promoter. Modifications of reporter gene imaging techniques have also been used to detect protein–protein interaction, which induces transcription of a reporter gene.

To image small animals, such as mice and rats, high resolution, preferably at a submillimeter level, is required. Resolution of small animal PET is limited by three factors: (1) positron range (see the

previous discussion), (2) noncollinear annihilation (see the previous discussion); and (3) intrinsic spatial resolution of the imaging device. By applying new techniques and materials, as described in the following discussion, FWHM of current small animal PET cameras has been refined to 2 mm, and further improvement of spatial resolution and sensitivity is expected. The new scintillator material lutetium oxyorthosilicate (LSO) possesses significantly higher scintillation efficiency and shorter light decay time than BGO, which is typically used in human scanners. These beneficial characteristics resulted in an increased counting rate and a reduction in random coincident rate. Conventional methods using a filtered back-projection algorithm are being replaced by iterative reconstruction methods to improve spatial resolution. To reduce errors caused by noncollinear annihilation and also to reduce cost, small animal PET devices have a small diameter, which makes the depth-of-interaction (DOI) effect significant. The DOI effect results in an increased uncertainty in the location of endpoints of the line of response connecting detector pairs. Several methods have been proposed to reduce DOI error, such as multiplayer scintillation crystal arrays in which the layer of interaction is determined by differences in light decay time between the scintillator in each layer.

As compared to in vitro and ex vivo autoradiography, which have higher spatial resolution, one advantage of small animal imaging is that it can provide pharmacokinetic information by repeated measurement in a single animal. On the other hand, one pitfall is that theories of pharmacology assume the use of negligible amounts of imaging ligand. If a large amount of imaging ligand is required to obtain adequate counts, this would violate assumptions of these theories. Assuming a consistent relationship between injected dose of radioligand and its concentration at the site of action, and using a method analogous to Michaelis-Menten equation kinetics, the following formula was derived to estimate receptor occupancy:

$$\text{Occupancy} = (\text{injected radioactivity})/(\text{body weight} \times \text{median effective dose } [ED_{50}] \times \text{specific activity} + \text{injected radioactivity})$$

To achieve low receptor occupancy in small animal imaging studies, high specific activity is required. A low level of receptor occupancy, which would fulfill tracer conditions, must be confirmed beforehand by estimating occupancy from specific activity and ED_{50}.

Although PET is clearly more advantageous than SPECT for achieving higher spatial resolution and high sensitivity, there have been some attempts to develop SPECT devices for small animal imaging.

Quantification of Receptor Densities In vitro receptor binding assays characterize receptors and ligands by measuring receptor density (B_{max}) and affinity (K_D). To obtain these measurements, various concentrations of radiolabeled and nonlabeled ligand must be used in the reactions. Although possible, it is usually difficult to measure each of B_{max} and K_D in human molecular imaging studies by administering various levels of ligands, because substantial levels of receptor occupancy can cause serious pharmacological effects. Limiting dose of ligand administration makes it impossible to measure each of B_{max} and K_D, and only a ratio of B_{max}/K_D (which equals specific binding distribution volume, V_S) can be measured. Therefore, in most human studies, V_S is the measure used to reflect changes in receptors and transporters. This ratio indicates that, when there is an increase in V_S, it is caused by an increase in B_{max} or a decrease in K_D.

Theoretical foundations for the calculation of V_S are beyond the scope of this chapter. Nevertheless, in brief, V_S is calculated as a ratio of specific binding in the brain to the parent ligand level in arterial plasma under equilibrium conditions (i.e., C_s^e/C_a^e, where C_s^e and C_a^e are the specific binding in the brain and the parent ligand level in arterial plasma under equilibrium conditions, respectively). An intuitive way of understanding V_S is that, under equilibrium conditions, specific binding in the brain is normalized to the radioligand level in arterial plasma. The level of specific binding in the brain is determined by the injected amount and the clearance of the radioligand, as well as the receptor parameter, B_{max}/K_D. For example, under tracer conditions, if the dose of injected radioligand is higher, specific binding in the brain becomes higher. Therefore, to measure the receptor parameter V_S, the level of specific binding in the brain needs to be normalized to the radioligand level in plasma.

The measurement of V_S requires accurate measurement of parent radioligand levels in plasma by metabolite analysis. A less labor intensive way to measure a receptor parameter is to calculate the ratio of specific to nonspecific binding under equilibrium conditions (i.e., C_s^e/C_{NS}^e, where C_{NS}^e is the nonspecific binding in the brain under equilibrium conditions). This parameter is often called the *binding potential* (*BP*). In analogy to V_S, an intuitive way to understand BP is that, under equilibrium conditions, the level of specific binding is normalized to that of nonspecific binding in the brain. If a greater amount of radioligand enters the brain, specific and nonspecific binding increase, and the level of specific binding is influenced by the amount of radioligand entering the brain. Therefore, to obtain measures that reflect binding of the targeted receptor or transporter, the level of specific binding needs to be normalized to the amount of the radioligand entering the brain. Hence, one must compare measures of nonspecific binding in a brain region that does contain a negligible level of the targeted receptor or transporter. For example, to study dopamine receptors, the cerebellum is often used as a region that contains few receptors. An assumption to use BP to compare groups of subjects is that, under equilibrium conditions, there is no difference in nonspecific binding per plasma radioligand level among groups. On the other hand, such an assumption is not required to use V_S.

This equilibrium ratio V_S is calculated through mathematical modeling or by experimentally achieving equilibrium conditions. In many studies, the radioligand is administered as an IV bolus. In such studies, brain and plasma parent ligand activity change dynamically over time, and a true equilibrium condition is never achieved (Fig. 1.16–6). In bolus injection studies, the ratio under equilibrium conditions, V_S, is calculated mathematically. There is another method to calculate V_S. Instead of calculating the equilibrium ratio V_S mathematically, the true equilibrium condition is achieved experimentally

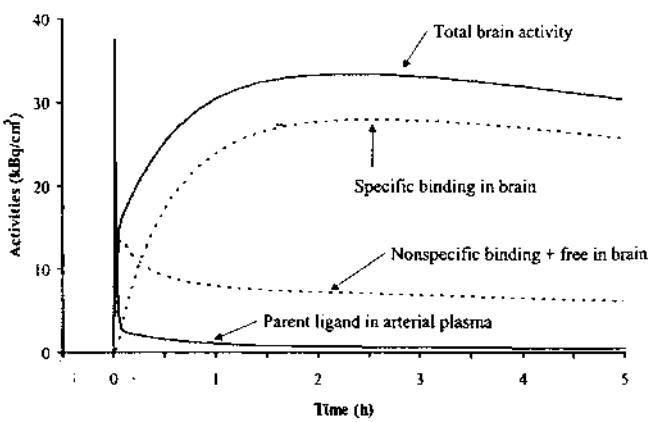


FIGURE 1.16–6 An example of brain and plasma parent ligand levels after a bolus injection. Levels of each component change dynamically over time. Note that all activities are decay corrected to time zero.

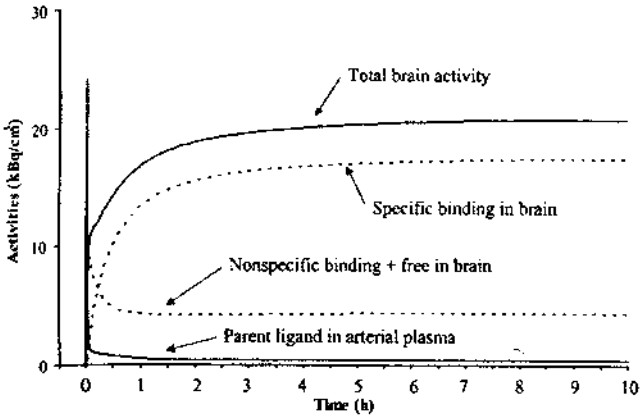


FIGURE 1.16–7 An example of brain and plasma parent ligand levels after a bolus injection and constant infusion. The same set of kinetic parameters is used to create curves of Figures 1.16–6 and 1.16–7. After prolonged infusion, an equilibrium condition is experimentally achieved—that is, all components reached stable levels. Note that all activities are decay corrected to time zero.

by performing an initial bolus injection of the radioligand, followed by a prolonged constant infusion (i.e., bolus plus constant infusion; Fig. 1.16–7). BP can also be calculated in these two ways—mathematically or experimentally.

SAFETY

With regard to studies in humans, PET and SPECT share similar safety concerns for radiation exposure and pharmacological toxicity of the injected radiopharmaceutical. The radiation exposures from typical PET and SPECT scans are thought to be reasonably safe within the context of present knowledge of radiation biology. The FDA has established limits of radiation exposure to various organs of the body and the body as a whole that are applied to research studies and that are often lower than exposures in routine clinical nuclear medicine procedures. Although the FDA limits are presently thought to provide adequate safety, the long-term biological effects of ionizing radiation remain an area of active investigation and even controversy. Although the estimation of the dose received by the body has multiple factors (including the amount of activity, the type of emission, and the residence time in the body), the shorter $T_{1/2}$ of PET radionuclides and the higher sensitivity of the method generally yield lower radiation burdens than a comparable SPECT study. A useful guideline is to use doses of radiotracer that are "as low as reasonably allowable" to provide useful results.

Fortunately, the pharmacological toxicity of radiopharmaceuticals is usually not a significant issue. The sensitivity of molecular imaging is so high that minuscule mass doses of compound may be injected, although that small mass is associated with significant levels of radioactivity. For example, some radiopharmaceuticals are injected at doses (in μg/kg and ng/kg) that are a millionfold lower than the minimal effective dose to cause any pharmacological effect. In such situations, no pharmacological toxicity would be expected, and only an unusual immunological adverse side effect could be anticipated. Nevertheless, the potential pharmacological effects and toxicity of radiopharmaceuticals need to be evaluated relative to previously established criteria for nonradioactive pharmaceuticals. Of course, the final formulation of any radiotracer must meet established guidelines for purity, sterility, and lack of pyrogenicity.

CLINICAL APPLICATION OF NEURORECEPTOR IMAGING

The use of PET and SPECT brain imaging can be roughly divided into measurements of local neuronal activity, neurochemistry, and in vivo pharmacology.

Local Neuronal Activity Local neuronal activity is directly correlated with energy consumption and can be calculated using (1) direct measures targeting glucose metabolism or (2) indirect measures of cerebral blood flow (CBF). Tandem fluctuations of CBF and glucose metabolism are regulated via an autoregulatory mechanism that has not yet been identified. Tracers used in PET imaging for measurement of local neuronal activity include [^{18}F]FDG (fluorodeoxyglucose) for glucose metabolism, and [^{15}O]H_2O for measures of blood flow. With regard to SPECT imaging, ^{99m}Tc- and ^{123}I-labeled agents, as well as ^{133}Xe gas, are used to calculate CBF, but no comparable tracer has yet been developed for glucose metabolism in SPECT imaging.

Neuronal metabolic demands are believed to reflect primarily terminal, rather than cell body, activity. This conclusion is based on a limited number of studies of nerve cells whose cell bodies are anatomically distant from their terminals. Given this hypothesis, in any specified volume of brain tissue, the majority of [^{18}F]FDG uptake in PET glucose metabolism studies is in the terminal, rather than in the cell body. Another important factor in understanding the big picture reflected by these measures is that metabolic analyses cannot distinguish activity of excitatory neurons from that of inhibitory neurons. Thus, although increased [^{18}F]FDG uptake is usually interpreted as a regional increase in functional activity, it may ultimately reflect overall systemic inhibition as a result of increased firing of inhibitory interneurons.

In the clinical setting, PET and SPECT are primarily used to target and to assess local neuronal abnormalities, including those associated with cerebral ischemia and epilepsy, and, furthermore, can also be used to distinguish radiation necrosis from tumor growth. These imaging results can significantly impact decisions on clinical care. For example, the neurosurgical treatment of patients with medically refractory epilepsy requires precise localization of seizure foci. Because foci are often distant from the surface of the brain, PET and SPECT modalities are uniquely suited for this task, and, in comparison, localization using scalp electrode electroencephalography (EEG) is crude. During the interictal period, the seizure focus is hypometabolic, exhibiting decreased blood flow. Conversely, blood flow increases in the focus during the ictal period, and the region becomes hypermetabolic. Thus, because of their dual use in assessment of glucose metabolism and blood flow, imaging with PET and SPECT not only has served as primary means of localization of seizure foci, but also confirm other diagnostic tests required to pinpoint the portion of the brain that is subsequently resected.

PET imaging using [^{15}O]H_2O has been elegantly used in neuropsychological activation studies to identify areas of the brain that perform cognitive and sensory functions, including reading, speaking, word association, visual identification, and spatial localization. The short $T_{1/2}$ of ^{15}O ($T_{1/2}$ of 2 minutes) is optimal for these studies, as it allows for multiple (often eight to ten) bolus injections of the tracer in one experimental session. Thus, baseline scans and those following neuropsychological tasks can be repeated and averaged.

PET imaging has also been used to determine the physiology and anatomy of depression. In patients diagnosed with major depression, neuronal activity assessments using measures of CBF glucose metabolism revealed decreased activity in several areas of the brain, includ-

ing regions of the frontal and temporal cortices and caudate nucleus. In familial major depressive disorders (unipolar or bipolar depression), metabolism in the prefrontal cortex, ventral to the genu of the corpus callosum (i.e., subgenual prefrontal cortex), was significantly lower as compared to controls. It was discovered, however, that gray matter volume in that region was less than normal and that, after corrections for volumetric differences were made, neuronal activity was actually higher in the patients than in healthy subjects. Thus, metabolism in the right subgenual prefrontal cortex correlates positively with depression severity, and this area, along with the other aforementioned brain regions, is now known to play a significant role in emotional processing. Further investigation of the anomalies in neural circuitry exposed by these imaging studies will hopefully lead to discovery of more precise mechanisms of the pathophysiology of depression and improved treatment of these disorders.

Neurochemistry Two important aspects in PET and SPECT imaging are high sensitivity and chemical selectivity, both of which are fundamental to reliable in vivo neurochemical measures. The sensitivity of PET and SPECT to detect radiotracers is less than 10^{-12} mol, which is several orders of magnitude greater than that of NMR methods. The term *sensitivity* refers to the minimal concentration of the tracer compound that can be reliably measured. For example, the minimal concentration of [^{11}C]chlorpromazine that can be measured with PET in the human brain within acceptable imaging time (e.g., 15 to 30 minutes) is less than 10^{-12} mol. In contrast, the minimal concentration of GABA that can be measured with magnetic resonance spectroscopy (MRS) is approximately 10^{-4} mol.

Radiotracers used to label specific target sites in the brain can be developed in a manner analogous to the development of therapeutic drugs selective for specific receptor sites. Radiotracers can then illuminate neurochemical pathways and mechanisms in the brain, including sites of neurotransmitter synthesis, reuptake and release, receptors, and metabolic enzymes. Additionally, researchers also hope to develop imaging techniques that could be used to investigate second messenger systems.

Of the various neurochemical systems in the brain, the greatest effort has been devoted to those that involve dopaminergic and serotonergic transmission. Current radiotracer development for these two systems focuses primarily on the pathophysiology of psychological disorders. The three principal research goals for these imaging studies are (1) to discover correlations between imaging results and clinical symptoms, (2) to measure effects of psychotropic or therapeutic drugs, and (3) to predict the clinical course of the disorder. However, except for imaging of the DAT in Parkinson's disease, existing neuroreceptor imaging agents have not demonstrated clinical usefulness for the diagnosis or management of neuropsychiatric disorders.

Dopamine Research for Parkinson's Disease 6-[^{18}F]Fluoro-L-3,4-dihydroxyphenylalanine ([^{18}F]FDOPA) has been used successfully in human studies to provide measures of dopaminergic terminals in the striatum. Results indicated significantly decreased striatal uptake in patients with Parkinson's disease compared to healthy subjects. Data from these studies have challenged the previously accepted notion that parkinsonian symptoms develop only after depletion of 85 to 90 percent of endogenous dopamine levels, as they illustrate that early signs of the disorder may appear after a decrease of only 50 to 60 percent in striatal dopamine terminal innervation. Conversely, studies of patients with schizophrenia revealed that neuroleptic-naive patients had an approximately 15 percent higher [^{18}F]FDOPA uptake in the putamen.

Dopamine Release A potential method for the measurement of neurotransmitter release requires that the endogenous transmitter displace the radiotracer from the cognate receptor. For example, endogenous dopamine can displace radiotracer binding to the D_2 receptor. Several in vivo labeling studies using rodents have shown that the resting levels of synaptic dopamine and stimulant-induced dopamine release are associated with significant D_2 receptor occupancy, which is mirrored by comparable displacement of radiotracer from the receptor. PET and SPECT D_2 receptor imaging studies in humans have incorporated a pharmacological challenge of dextroamphetamine—a substance that facilitates a massive release of dopamine into the synapse. These studies have shown that the amount of displacement in healthy subjects is correlated with neuronal excitation and subjective reports of euphoric state. Similar studies of schizophrenia patients using [^{123}I]iodo-2-hydroxy-6-methoxy-*N*-([1-ethyl-2-pyrrolidinyl]methyl)benzamide ([^{123}I]IBZM) as a D_2 receptor ligand have revealed that the amount of dopamine released is two and one-half times higher than that in healthy subjects (Fig. 1.16–8) and that the amount of the release is correlated with a transient increase in positive symptoms (Fig. 1.16–9). The same method was applied to a study of unipolar depressed patients that found unaltered release of dopamine. Another study looked at resting levels of dopamine in the synapse. Comparisons of D_2 receptor availability measures before, and during, α-methyl-*para*-tyrosine–induced dopamine depletion were performed on data from schizophrenia patients and healthy controls. Elevated synaptic dopamine was observed in patients and correlated with good response of positive symptoms to antipsychotic drugs. These imaging studies have provided further evidence of dopamine's role in psychotic symptoms.

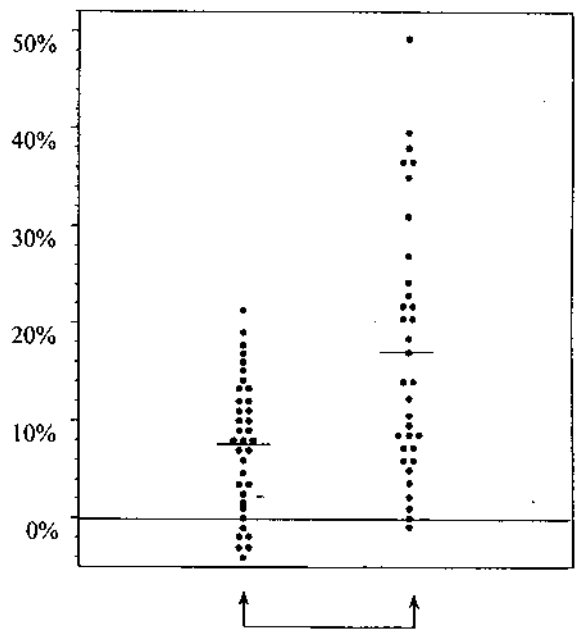


FIGURE 1.16–8 Effect of amphetamine (0.3 mg/kg) on [^{123}I]iodo-2-hydroxy-6-methoxy-*N*-([1-ethyl-2-pyrrolidinyl]methyl)benzamide([^{123}I]IBZM) binding in healthy control subjects and untreated patients with schizophrenia. The y-axis shows the percentage decrease in [^{123}I]IBZM binding potential induced by amphetamine, which is a measure of the increase occupancy of dopamine type 2 receptors by dopamine after the challenge. (From Laruelle M, Abi-Dargham A, Gil R, et al.: Increased dopamine transmission in schizophrenia: Relationship to illness phases. *Biol Psychiatry.* 1999;46:56, with permission.)

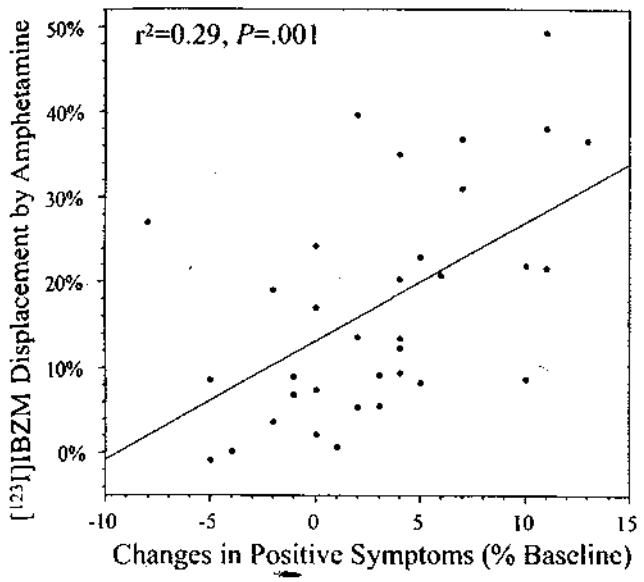


FIGURE 1.16–9 Relationship between striatal amphetamine-induced dopamine release and amphetamine-induced changes in positive symptoms. [^{123}I]IBZM, [^{123}I]iodo-2-hydroxy-6-methoxy-*N*-([1-ethyl-2-pyrrolidinyl]methyl)benzamide. (From Laruelle M, Abi-Dargham A, Gil R, et al.: Increased dopamine transmission in schizophrenia: Relationship to illness phases. *Biol Psychiatry.* 1999;46:56, with permission.)

Receptors Among all of the potential targets of neurochemical imaging, receptors have probably received the most attention. If a receptor is selectively altered in a specific disease, then imaging of this site may provide diagnostic information about the disorder.

DOPAMINE TYPE 1 (D_1) RECEPTOR Because of its role in cognitive function in the prefrontal cortex and occupancy by some antipsychotic drugs, the dopamine type 1 (D_1) receptor has received considerable attention. Among the receptor ligands developed for D_1-like receptors (D_1 and D_5 subtypes), [^{11}C]SCH23390 came first. In the initial human study using this radiotracer, schizophrenic patients showed lower D_1 receptor binding in the prefrontal cortex as compared to controls, and these lower measures correlated with negative symptoms of the disease.

Later, a more selective D_1 radiotracer, [^{11}C]NNC-112, was developed and used in schizophrenia studies. This tracer yields a higher ratio of specific to nonspecific uptake than [^{11}C]SCH23390 and is able to provide measures of D_1 receptors in low-density regions. As opposed to [^{11}C]SCH23390, [^{11}C]NNC-112 showed a moderate *increase* in receptor binding in the dorsolateral prefrontal cortex of patients with schizophrenia. This increase was negatively correlated with patients' performance on a working memory task. Researchers hypothesized that increased prefrontal D_1 receptor binding was a compensatory upregulation resulting from long-term decreases in dopamine innervation of the cortex, but future studies are needed to solidify and confirm this important conjecture.

DOPAMINE TYPE 2 (D_2) RECEPTOR The D_2 receptor, a known target of antipsychotic drugs, was the first receptor to be extensively studied with preponderance on schizophrenia beginning in the 1980s. Initial studies investigated baseline levels of D_2 receptor binding, looking for differences between normal patients and patients with schizophrenia. Contradictory findings were reported by investigators in the United States (elevated striatal D_2 receptors) and in Sweden (no elevation). Although this controversy is still not completely resolved, the general consensus is that schizophrenia is associated with no or, at most, small elevations of striatal D_2 receptor binding.

Subsequent studies have focused on endogenous measures of dopamine itself (see the previous discussion) or on development of new PET tracers for quantification of low-density D_2 receptors found in extrastriatal regions, such as the temporal cortex. Among the newly discovered PET ligands are agents, such as [^{18}F]fallypride and [^{11}C]FLB-457, both of which have demonstrated low enough nonspecific uptake so as not to obscure low levels of receptor binding in cortical regions. More recently, in drug-naive schizophrenia patients, [^{11}C]FLB-457 binding in the anterior cingulate was found to be lower compared to measures in healthy controls. Current trends in research convey increasing interest in extrastriatal D_2 receptors, and the results of these studies are anticipated in the near future.

SEROTONIN TYPE 1A (5-HT_{1A}) RECEPTOR The serotonin type 1A (5-HT_{1A}) receptor is found at postsynaptic sites in areas such as the hippocampus and at presynaptic sites on 5-HT neurons in the dorsal raphe nucleus of the midbrain. In presynaptic (i.e., somatodendritic) locations, the 5-HT_{1A} receptor functions as an inhibitory autoreceptor to decrease 5-HT neural firing, thereby reducing the release of 5-HT at distal terminal regions. Animal and human studies suggest that the 5-HT_{1A} receptor may play a critical role in the mechanisms of action of selective serotonin reuptake inhibitors (SSRIs). During the first few weeks of SSRI treatment, the postsynaptic 5-HT_{1A} receptor is thought to increase in sensitivity as the 5-HT_{1A} presynaptic autoreceptor decreases in functional activity. The net result is a marked enhancement in 5-HT neurotransmission: enhanced postsynaptic activity and decreased autoinhibition. This fundamental outcome has made the 5-HT_{1A} receptor subtype a popular target of PET imaging, especially with regard to mood disorder research. This receptor is a major player in the regulation of serotonergic neuronal activity. Abnormalities in this receptor have been inferred by clinical observations of treatment of major depression. ^{11}C-labeled WAY-100635 (*N*-[2-(4-[2-methoxyphenyl]-1-piperazinyl)ethyl]-*N*-[2-pyridyl] cyclohexane carboxamide) was developed expressly for 5-HT_{1A} receptor imaging. Results from two PET studies using this radiotracer indicated reduction in receptor binding in patients with unipolar major depression. One of these studies indicated more pronounced reduction in the presynaptic region (dorsal raphe), whereas both studies demonstrated moderate reduction in the postsynaptic regions (neocortex and hippocampus). Furthermore, one study showed minimal change in the receptor after chronic SSRI treatment, suggesting that binding decreases are a trait-dependent, rather than a state-dependent, abnormality.

Transporters In addition to receptors, transporters (reuptake sites) have also been imaged.

DOPAMINE TRANSPORTER When dopamine is released from neuron terminals into the synaptic cleft, this chemical signal is deactivated by reuptake into presynaptic terminals by the DAT. This transporter plays a fundamental role in affecting the physiological and subsequent psychological outcomes of therapeutic agents and drugs of abuse. For example, amphetamine causes DAT to operate in reverse, thereby ejecting large quantities of dopamine into the synapse. Cocaine and methylphenidate act to halt the function of DAT, leading to a buildup of dopamine in the synaptic cleft.

Several radiotracers have been developed for DAT, including: [^{11}C]cocaine, [^{11}C]methylphenidate, 2β-carbomethoxy-3β-(4-fluorophenyl) tropane ([^{11}C]CFT) (also designated *WIN 35,428*), and (1*R*)-2β-carbomethoxy-3β-(4-iodophenyl) tropane ([^{123}I]β-CIT), which is also designated *RTI-55*. Research involving these new tracers has

shown that striatal uptake of [^{11}C]CFT and [^{123}I]β-CIT is markedly decreased in patients with Parkinson's disease in comparison to healthy subjects of similar age. Although much is still to be learned, DAT imaging with these tracers offers new hope for early diagnosis and tracking disease progress. Additionally, a new SPECT tracer for DAT was recently approved for use in the European Union to aid in the diagnosis of Parkinson's disease.

In another realm of current research, [^{123}I]β-CIT and other tropane analogs are being used to investigate DAT function in psychiatric disorders, such as schizophrenia, acute cocaine abstinence, and Tourette's syndrome. In patients with schizophrenia, no apparent change was observed in levels of DAT protein, which have been imaged and quantified with SPECT or PET. Imaging in abstinent cocaine addicts has shown contradictory results of increased, versus decreased, DAT binding. However, this discrepancy could be caused by inconsistencies in subject selection concerning the period after cocaine discontinuation. Immediately after discontinuation, DAT levels may be elevated, and these elevations reflect changes stemming from a short-term physiological adaptation responding to the abruptly unmet demands of a firmly established chronic DAT blockade. Finally, in at least two studies of Tourette's syndrome, reports have shown significant (35 percent) elevations of DAT levels in the striatum. Elevated levels in this context may reflect enhanced dopamine neurotransmission in this disorder and may be the key to the partial success of dopamine blocking therapies, as with neuroleptic medications.

Serotonin Transporter Similar to mechanisms involved in termination of dopamine synaptic signaling, the activity of 5-HT is terminated by its reuptake into 5-HT terminals via the serotonin transporter (SERT). The antidepressant actions of SSRIs are mediated by a SERT blockade, thereby leading to a buildup of 5-HT in the synapse. SERT imaging may be important to elucidate the pathophysiology of the disorder and to monitor treatment. Before the recent development of PET radiotracers selective for SERT, [^{123}I]β-CIT and other tropane analogs that bind SERT *and* DAT have been studied in patients with depression. Despite their lack of selectivity, the inherent difference in regional distributions of DAT and SERT has made it possible to arrive, at least, at ballpark measures of each transporter type. The binding of [^{123}I]β-CIT predominantly reflects SERT in midbrain and diencephalon and DAT in striatum. In reference to clinical symptoms, these data have inferred irregularities of SERT in several disorders, including alcoholism, major depression, and cocaine abuse. In an early study in patients with major depression, midbrain SERT binding was found to be lower in patients as compared to healthy controls. In patients with behavioral problems, such as binge eating and impulsivity, lower SERT binding was found by using the radiotracer. Still, one must remember that these are no more than rudimentary applications and that cross-reactivity of these tropane analogs with SERT and DAT precludes a precise measurement of SERT levels. Fortunately, more selective SERT ligands have recently been developed and will provide valuable information on this target for mood and other psychiatric disorders. An initial report of one of these new selective agents, *N,N*-dimethyl-2-(2-amino-4-cyanophenylthio) benzylamine ([^{11}C]DASB), found no change in SERT levels in frontal cortex, caudate, or thalamus.

Metabolism The fate of a neurotransmitter can be studied by injection of selective inhibitors of its catabolic enzymes. For example, ^{11}C-labeled suicide enzyme inactivators, clorgyline and L-deprenyl, are used to image monoamine oxidase (MAO) types A and B, respectively. In this regard, PET imaging unexpectedly revealed that cigarette smoking significantly inhibits MAO activity in brain, presumably by some agent other than nicotine in the smoke.

Amyloid-β Deposits Alzheimer's disease is a devastating disorder for which no effective therapy is currently available. Diagnosis depends on the clinical symptoms, such as severe impairment of memory function. The brain tissue of patients is characterized by the deposition of neurofibrillary tangles and amyloid-β plaques. Subjective diagnosis would be made if these pathological changes could be imaged in vivo. The dependence of the diagnosis on the clinical symptoms and the necessity of a subjective tool of diagnosis, which molecular imaging would provide, are similar to those for Parkinson's disease before the development of [^{18}F]FDOPA and selective radioligands for DAT. Development of imaging agents for amyloid-β deposits will be the needed breakthrough for the diagnosis of Alzheimer's disease, just as the dopamine terminal imaging agents were for Parkinson's disease. Additionally, enormous effort is also being made to delay or even reverse the progress of Alzheimer's disease by using medications that stop deposition of or even remove amyloid-β deposits. Therefore, imaging agents for amyloid-β deposits will also provide tools to track progress of such therapies, as well as to diagnose the disease. From this perspective, such imaging agents may also follow the same path of clinical use as dopamine terminal imaging agents, which now provide a means to monitor implanted cells in Parkinson's diseased patients and to monitor possible delays of the progress of disease by new therapeutics. After years of trials based on the structures of dyes used in postmortem studies, some progress is now being seen with radioligands, developed during the first years of this century, that show hope for successful imaging of amyloid-β deposits in vivo.

Intracellular Signal Transduction Systems Although only a limited number of studies have been performed in human subjects, attempts to image intracellular signal transduction systems should be noted. Cyclic adenosine monophosphate (cAMP) and phosphoinositides are two major second messengers in neurotransmission systems, and arachidonate also plays a role in intracellular signal transduction systems. [^{11}C]Rolipram is the most widely used ligand for signal transduction system imaging. This ligand is an inhibitor of phosphodiesterase IV, which specifically metabolizes cAMP in the brain. Therefore, the binding of [^{11}C]rolipram reflects levels of the feedback system of the cAMP pathway. Other, less widely used tracers are [^{11}C]diacylglycerol and [^{11}C]arachidonate. Injected [^{11}C]diacylglycerol is incorporated into phosphoinositides and is expected to reflect their turnover.

In Vivo Pharmacology

Because receptors are frequently the targets of therapeutic medications, several investigators have argued that receptor imaging may be used to monitor drug treatment more accurately than is possible with measurement of plasma levels of the medications. However, the rationale for this argument is flawed from the theoretical perspective. Under steady-state conditions achieved with long-term treatment, the level of free (i.e., not protein bound) drug in plasma should achieve equilibrium with the free level of drug in the extracellular space of the brain. Thus, under steady-state conditions, there is little apparent value in performing expensive neuroreceptor imaging studies instead of simple measurements of the free level of drug in plasma. However, for non–steady-state conditions (e.g., beginning or discontinuing treatment), receptor imaging can provide valuable kinetic information.

The brain uptake and washout of many psychoactive agents can be markedly delayed compared to the rapid peak and fast clearance of the drug from plasma. For example, the maximal brain uptake of the potent cocaine analog, cocaine-iodo-tropane, occurs approximately 12 hours after IV administration as compared to plasma levels, which peak at 2 minutes. In addition, significant D_2 receptor occupancy has been reported to last for several weeks after discontinuation of antipsychotic agents, even when plasma levels are almost undetectable.

Several pharmaceutical companies and academic researchers have begun to explore the role of receptor imaging in new drug development. Two fundamental methods used in this investigation are (1) the radiolabeling of a target compound (e.g., labeled with ^{11}C) and (2) the in vivo screening of the effects of IV administered nonradioactive compounds with previously developed radiotracers. An example of the first method would be the use of ^{11}C-labeled fluoxetine (Prozac); an example of the second method would be the use of nonradioactive fluoxetine that would interact with another radiolabeled probe (e.g., [^{11}C]DASB for SERT).

Antipsychotic occupancy of the D_2 receptor has been extensively investigated using [^{11}C]raclopride. Studies have demonstrated occupancy of the D_2 receptor by typical and atypical antipsychotic medications, such as haloperidol (Haldol), clozapine (Clozaril), quetiapine (Seroquel), risperidone (Risperdal), olanzapine (Zyprexa), and loxapine (Loxitane). Data have shown that D_2 receptor occupancy of therapeutic doses of atypical antipsychotic agents is lower (approximately 40 to 60 percent) than with comparable doses of typical neuroleptic medications (70 to 90 percent). The lower incidence of extrapyramidal symptoms with atypical agents may be due, in part, to their lower D_2 receptor occupancy.

In a similar manner, SERT occupancy by SSRIs has been measured by using PET. Recent studies have shown that even low doses of SSRIs cause nearly complete (80 to 90 percent) occupancy of brain SERT. This conclusion, in turn, now raises the question of the functional usefulness of higher SSRI doses. However, as in most avenues of research, many new questions arise in the search for empirical confirmation of current hypotheses, and, thus, knowledge is refined, and improved clinical treatment of disease is pushed ever closer.

SUGGESTED CROSS-REFERENCES

Brain-imaging techniques are discussed in Section 1.15. Electrophysiology in clinical practice is discussed in Section 1.14, and neuroimaging in geriatric assessment is discussed in Sections 51.2e and 51.2f. The other sections of Chapter 1 discuss related neural sciences, particularly Section 1.2 on functional neuroanatomy and Section 1.14 on applied electrophysiology.

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